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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/720,326	Applicant(s) SATO ET AL.	
	Examiner Karen A Canella	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,4 and 6-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,4 and 6-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 16, 2003 has been entered.

2. Please note that the examiner assigned to this application has been changed.

3. Claims 1, 4, 6 and 7 have been amended. Claims 9-33 have been added. Claims 1, 4 and 6-33 are pending and under consideration.

4. Claims 1, 4 and 6-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 13 and 22 recite "a patient suffering from or susceptible to hypercalcemic crises associated with impaired consciousness". It is unclear if the requirement of the claim is that the patient be actually exhibiting impaired consciousness at the time of treatment. for purpose of examination, both treatment at the time of impaired consciousness and treatment as a prophylactic measure against the risk of impaired consciousness will be considered.

Claim 1 recites "allowing the antibody to inhibit the binding of PTH-rP to a receptor thereof; decreasing a blood calcium level by at least 1 mg/dl...and maintain the at least 1 mg/dl decrease in blood calcium level". It is unclear how "a blood calcium level" relates to the method preamble of treating a patient. It is unclear how the method step of "decreasing a blood calcium level" and "maintaining the at least 1 mg/dl decrease" is related to the administration of the humanized anti-PHT-rP antibody.

It is unclear how claim 4 further limits claim 1 as the property of inhibiting the binding between PTH-rP and a receptor thereof recited in claim 4, is a limitation of the antibody recited in claim 1.

Claim 33 recites "the method according to claim 2". Claim 2 has been canceled. for purpose of examination, the claim will be read as depending on claim 1.

It is unclear how claim 7 further limits the scope of claim 1 and how claim 17 further limits the scope of claims 13 or 14, and how claim 28 further limits the scope of claims 22 or 25. Claim 1 encompasses a humanized anti-PHT-rP antibody. Claims 7 , 17 and 28 embody the independent claims, 13, 14, 22 or 25, wherein the antibody is a monoclonal antibody. It would be inherent that the humanized antibodies of claims 1, 13, 14, 22 or 25 were also monoclonal antibodies.

Claims 6, 16, and 27 are vague and indefinite in the recitation of #23-57-137-1 as the only means of identifying the monoclonal antibody on which the claims depend. #23-57-137-1 is a laboratory designation which can be easily confused with the same designation assigned to a completely different product. Amendment of the claims to recite the Deposit Accession Number would overcome this rejection, because Deposit Accession Numbers are unique identifiers.

5. Claims 13-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Claim 13 has incorporated the limitation of decreasing a blood calcium level to at least 15 mg/dl to effectively treat the patient. Neither the specification nor claims as filed provide support for the specific limitation of 15 mg/dl. Claim 22 is broadly drawn to "decreasing a blood calcium level to effectively treat a patient". the specification (page 6, lines 6-22) describe a method wherein an agent of the instant invention can be used to decrease the corrected serum calcium level by 1 gm/dl or 2 mg/dl, in 24, 6 or 4 hours after administration of the agent. these are very specific values for decreasing the corrected serum calcium level and as such do not provide support for the broader claim drawn to "decreasing a blood calcium level to effectively treat the patient". Further, claim 22 specifies a method for treating a patient suffering from drug-resistant hypercalcemic crisis. the specification states (page 3, lines 12-23) that calcitonin, bisphosphonate, phosphate buffer, physiological saline, furosemide is administered to improve

hypercalcemia, but that these drugs can cause adverse side affects and the development of pharmacological effects may be delayed. The specification concludes that drugs having higher therapeutic effects and fewer side effects are desirable. The specification suggests the use of the instant invention which is satisfactory as a safe, prompt therapeutic agent for hypercalcemic crises. the specification makes no mention of using the instant methods a s "fall back" in the case that the hypercalcemia is resistant to calcitonin, furosemide, etc. The specification teaches the prompt use of the agents of the instant invention, , therefore teaching against the use of the conventional means of treatment prior to the administration of the antibody of the instant invention. Thus one of skill in the art would conclude that applicant as not in possession of the instant invention at the time of filing.

6. Claims 1, 4, 6-21 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claim 1 is drawn to a method for treating a patient suffering from or susceptible to hypercalcemic crisis associated with impaired consciousness comprising administering a humanized anti-PTH-rP antibody capable of inhibiting the binding between PTH-rP to a receptor thereof; decreasing and maintaining the blood calcium level by 1 mg/dl. Claim 33 embodies the method of claim [1] wherein the blood calcium level is decreased by at least 2 mg/ dl. Potts teaches that when serum calcium levels are 15 mg/dl to 18 mg/dl or higher, coma and cardiac arrest can occur. A reduction of only 1 mg/dl or2 mg/dl at the minimum danger level of 15 mg/dl will not reduce the calcium level in the blood of said patient to the to the point at which the patient is out of danger for cardiac arrest and coma. Claim 13 is drawn to a method of treating a patient suffering from or susceptible to hypercalcemic crises associated with impaired consciousness comprising administering to a patient a humanized anti-PHT-rP antibody inhibiting the binding between PTH-rP and a receptor thereof, allowing the antibody to inhibit the binding of PTH-rP and "a" receptor thereof, decreasing a blood calcium level to at least 15 mg/dl to effectively treat the patient. Potts (cited above) teaches that when serum levels reach 15 to 18 mg /dl or higher, coma and cardiac arrest can occur. (page 1902). The recited limitation of

decreasing the blood calcium level to 15 mg/dl does not decrease the calcium level to the point at which the patient is out of danger for cardiac arrest and coma. Thus, one of skill in the art would not be able to use the claimed method

7. Claims 1, 4 and 6-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating a patient suffering from or susceptible to hypercalcemic crises a s a result of elevated levels of PHTrP, does not reasonably provide enablement for methods of treating hypercalcemic crises having increased calcium levels from other causes than elevated levels of PHTrP The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims..

The claims are drawn to a method for treating a patient suffering from or susceptible to hypercalcemic crises comprising the administration of a humanized anti-PTHrP antibody. It is well known in the art that hyperglycemia can be caused by a multitude of factors. for instance Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's Principles of Internal Medicine, 12th Edition, pages 1902-1915) teaches that primary hyper parathyroidism results in an increased secretion of parathyroid hormone (page 1902, second column, bridging sentence to page 1903, first column, line 3). In the case of primary hyperparathryoidism it would not be expected that administration of an antibody which would specifically bind to the parathyroid hormone-related-peptide would bind to parathyroid hormone. Potts identifies familial hypocalciuric hypercalcemia in which affected individuals have persistent hypercalcemia without elevated levels of PTH (page 1906, second column) ; vitamin-D related hypercalcaemia due to vitamin d intoxication or sarcoidosis or other granulomatous diseases (page 1908, second column); hypercalcaemia associated with rapid bone turnover due to hyperthyroidism (page 1909, second column); hypercalcaemia associated with renal failure (pages 1910-1911). Potts et al teach that malignancy-related hypercalcemia is caused by a humoral factor which is distinct from PTH (page 1907, first column, last sentence of the fourth paragraph under the heading "Malignancy related hypercalcemia"). Potts et al teach that the histological characteristic of the tumor is important in predicting hypercalcemia and that patients with squamous cell carcinoma of the lung or renal tumors result in a high percentage of patients

who develop hypercalcemia in contrast to small cell and adenocarcinoma of the lung which rarely produces hypercalcemia (page 1907, first column, last full paragraph and bridging paragraph). Potts et al teach that PTH-related peptide fulfills the criteria of a humoral agent for the hypercalcaemia syndrome that is similar to but distinct from PTH (page 1910, first column, lines 1-9). One of skill in the art would not be able to treat hypercalcemia by the administration of an antibody which binds to PTH related peptide in individuals not exhibiting elevated levels of PTH-rP. this is confirmed by Sato et al (Journal of Bone and Mineral Research, 1993, vol. 8, pp. 849-860, cited in a previous Office action) who specifically teach that passive immunization of a hypercalcemic mouse bearing a transplanted parathyroid carcinoma which secretes PTH rather than PTH-rP, did not effect the blood calcium serum concentration. Sato et al concludes from this observation that it is PTH rather than PTH-rP which controls the serum calcium levels in primary hyperparathyroidism (page 858, second column, first full paragraph). Thus it would be undue experimentation without reasonable expectation of success in order to practice the broadly claimed invention for the treatment of hypercalcemia of any etiology.

8. Claims 22-26, 28-31are rejected under 35 U.S.C. 103(a) as being unpatentable over Seger et al (US 5,494,806) in view of Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915, IDS reference) and Schlom (In: Molecular foundations of Oncology, Sameule Broader, Ed, 1991, pages 95-134).

Claim 22 is drawn to a method for treating a patient suffering from or susceptible to hypercalcemic crises associated with impaired consciousness comprising administering to said patient a humanized anti-PTHrP antibody capable of inhibiting the binding between PTH-rP and a receptor thereof; allowing the antibody to inhibit the binding of PTH-rP and a receptor thereof and decreasing a blood calcium level to effectively treat a patient suffering from or susceptible to drug-resistant hypercalcemic crises associated with impaired unconsciousness, comprising administering to a patient a humanized anti-PTH-rP antibody inhibiting the binding between PTH-rP and a receptor thereof, allowing the antibody to inhibit the binding of PTH-rP and a receptor thereof decreasing a blood calcium level to effectively treat the patient Claim 28 embodies the method of claim 22 or 25 wherein the antibody is a monoclonal antibody. Claim

23 embodies the method of claim 22 wherein the drug-resistant hypecalcemic crises is defined as a blood calcium level that does not normalize after 24 hours of treatment and remain normal over at least 24 hours with one of the therapeutic drugs chosen from biphosphonate, calcitonin, a steroid, a phosphate buffer physiological saline and furosemide. Claim 25 embodies the method of claim 22 wherein the patient is administered at least one fragment of the humanized anti-PTHrP antibody. claim 26 embodies the method of claim 25 wherein the fragment is Fab, scFv, F(ab')2 and Fv. Claim 29 embodies the method of claim 22 wherein the hypercalcemic crises is associated with malignant tumor. claim 30 embodies the method of claim 22 wherein the hypercalcemic rises is associated with at least one of coma or cardiac arrest, Claim 31 embodies the method of claim 22 or 25 wherein the antibody is bound to a carrier.

Segre et al (U.S. 5,494,806) teach a method for rapidly intervening in a patient exhibiting hypercalcemia comprising the administration of antagonists of PTHrP (column 24, lines 35-41). Segre et al teach that such antagonists include compounds which interfere with the PTH receptor-mediated activation and that the appropriate antibody antagonist or peptide antagonist is administered at a dosage that provides adequate competition for PTHrP binding to the PTH receptor and that this will correspond to the dosage sufficient to lower the calcium level to below 10 mg/dl (column 24, lines 41-51), thus fulfilling the specific embodiment of treating a patient susceptible to hypercalcemic crisis associated with impaired consciousness comprising administering to said patient a anti-PTHrP antibody inhibiting the binding between PTHrP and the PTH receptor and allowing the antibody to inhibit the binding of PTHrP to the PTH receptor and decreasing a blood calcium level to effectively treat said patient. Segre et al teach that the antibody can be formulated in a carrier (column 24, lines 45-46) thus fulfilling the specific embodiment of claim 31. Segre et al teach that treatment may be repeated as necessary for long term maintenance of acceptable calcium levels of less than 10.1 mg/dl (column 24, lines 52-55) thus fulfilling the specific embodiment of claim 24 wherein the normal blood calcium level is less than 12 mg/d. Segre et al teach that the antibodies and other compounds of the invention are useful for the treatment of disorders characterized by the interaction between a cell receptor of the invention and a ligand (column 23, lines 25-40). Segre et al teach that hypercalcemia mediated by PTHrP results from humoral hyerpcalcemia of malignancy (column 23, lines 46-47) thus fulfilling the specific embodiment of claim 29 drawn to a malignant tumor. Segre et al

teach that compounds, including antibodies and polypeptide, may be screened for their agonistic or antagonistic properties using the cAMP accumulation, intracellular calcium, and/or inositol phosphate assays as specifically described (columns 22, line 65-column 23, line 22). Segre et al do not specifically teach a humanized PTHrP, treating a patient who is undergoing a drug-resistant hypercalcemic crises associated with impaired consciousness.

Potts teaches that severe hypercalcemia, usually defined as 15 mg/dl or above is a medical emergency, and that coma or cardiac arrest can occur when serum calcium levels are at 15 to 18 mg/dl or higher. Potts teaches rehydration with saline as a therapeutic agent (pages 1912-1913, under the heading , and therefore fulfills the specific embodiment of physiological saline. Potts teaches phosphate administered intravenously as a therapeutic agent(pages 1913-1914, under the heading "Phosphate") and biphosphonates (page 1913, first column,), fulfilling the specific embodiment of a biphosphonate, as well as glucocorticoids (a steroid) and calcitonin (page 1913, second column). Potts does not specifically teach a drug-resistant or a therapeutic agent resistant hypercalcemic crises..

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of murine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the murine antibodies (pages 97-98, bridging paragraph). Schlom also teaches that F(ab')2 or Fab' fragments also help reduce the HAMA response (page 119 second column, lines 16-17 under the heading "Single Chain Antigen Binding Proteins). Schlom also teaches that scFv although comparable in binding affinity to FAb' have a more rapid plasma clearance than the Fab' fragment resulting in a greater tumor to tissue ratio. Schlom also points out that the small size of the scFv improves the capacity for penetration through the tumor mass.. Schlom also points out that scFv are easier to make than F9ab')2 of Fab' fragments.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to treat a patient undergoing hypercalcemic crisis wherein said crises was manifest by coma or cardiac arrest by the administration of a humanized anti-PTHrP

antibody which is an antagonist of PTHrP binding to the PTH receptor in order to lower blood calcium to normal levels. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Seger et al on the method of treating patients needing immediate intervention because elevated serum calcium level can be fatal; and the teachings of Potts regarding the risk of coma or cardiac arrest in individual having serum calcium levels of 15 mg/dl to 18 mg/ dl or higher. It would also be obvious to use a fragment of the antibody such as scFv for maximum penetration into the tumor vasculature.

Potts teaches the therapeutic agents as set forth in claim 23. None of the references specifically teach the therapeutic intervention of hypercalcemic crisis after the therapeutic agents as taught by Potts et al fail: However, one of skill in he art would be motivated to administer the antibody to patients having drug-resistant hyper calcium because it is an emergency situation, and the antibody can directly antagonize the action of the PTH receptor. One of skill in the art would be motivated to find a molecular means of intervention that was unrelated to the molecular mechanism of action of the drug or therapeutic agent which failed to maintain the patients serum calcium level within the normal range.

9. Claims 22-26, 28-32are rejected under 35 U.S.C. 103(a) as being unpatentable over Seger et al (US 5,494,806) and Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915) and Schlom (In: Molecular foundations of Oncology, Sameule Broader, Ed, 1991, pages 95-134). as applied to claims 22-26, 28-31 above, and further in view of Gristina et al (5,681,565). The specific embodiments of claims 22-26, 28-31 and the teachings of Segre et al, Potts and Schlom which render obvious said embodiments are set forth above. None of the cited reference specifically teach the antibody bound to the carrier PEG.

Gristina et al teach that antibodies can administered in a creme or ointment carrier such as oleaginous bases or polyethylene glycol for in situ use (column 5, lines 3-21).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention to use PEG as a carrier. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Grishina et al on the effectiveness of PEG as a carrier for in situ administration of antibodies.

10. Claims 22-23, 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Sato et al (WO 9813388, IDS reference) in view of Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915). The specific embodiments of claims 22-24 and 28-30 are set forth above. Claim 27 embodies the method of claim 22 wherein the antibody is humanized #23-57-137-1.

The abstract of Sato et al teaches the humanized #23-57-137-1 monoclonal antibody. The abstract teaches that the humanized antibody can be used to treat hypercalcemia and other disorders caused by cancer. The abstract does not teach that the humanized #23-57-137-1 monoclonal antibody would inhibit the binding of the PTHrP and the PTH receptor, however, the antibody is identical to the specific embodiment of claim 27, therefore said antibody must have the inherent characteristic of inhibiting the binding of PTHrP to the PTH receptor. The abstract does not specifically teach drug-resistant hypercalcemic crisis associated with impaired consciousness, wherein the hypercalcemic crises is defined as a blood calcium level that does not normalize after 24 hours of treatment and remain normal over at least 24 hours with one of the therapeutic agents chosen for biphsophonate, calcitonin, a steroid, phosphate buffer, physiological saline and furosemide.

Potts teaches that severe hypercalcemia, usually defined as 15 mg/dl or above is a medical emergency, and that coma or cardiac arrest can occur when serum calcium levels are at 15 to 18 mg/dl or higher. Potts teaches rehydration with saline as a therapeutic agent (pages 1912-1913, under the heading , and therefore fulfills the specific embodiment of physiological saline. Potts teaches phosphate administered intravenously as a therapeutic agent(pages 1913-1914, under the heading "Phosphate") and biphosphonates (page 1913, first column,), fulfilling the specific embodiment of a biphosphonate, as well as glucocorticoids (a steroid) and calcitonin (page 1913, second column). Potts does not specifically teach a drug-resistant or a therapeutic agent resistant hypercalcemic crises..

Potts teaches that the humoral mediator of malignancy associated hypercalcemia is PTHrP. Potts teaches that this mediator competes with PTH for occupancy of the PTH receptor and induces hypercalcemia in test animals, and that the data indicate that PTHrP acts through

activation of the PTH receptor(page 1908, first column, lines 2-9). Potts teaches the therapeutic agents as set forth in claim 23. None of the references specifically teach the therapeutic intervention of hypercalcemic crisis after the therapeutic agents as taught by Potts et al fail: However, one of skill in he art would be motivated to administer the antibody to patients having drug-resistant hypercalcium because it is an emergency situation, and the antibody can directly bind to the humoral mediator of the hypercalcemia, PTHrP. One of skill in the art would be motivated to find a molecular means of intervention that was unrelated to the molecular mechanism of action of the drug or therapeutic agent which failed to maintain the patients serum calcium level within the normal range.

Potts teaches rehydration with saline as a therapeutic agent (pages 1912-1913, under the heading , and therefore fulfills the specific embodiment of physiological saline. Potts teaches phosphate administered intravenously as a therapeutic agent(pages 1913-1914, under the heading "Phosphate") and biphosphonates (page 1913, first column,), fulfilling the specific embodiment of a biphosphonate, as well as glucocorticoids (a steroid) and calcitonin (page 1913, second column). Potts does not specifically teach a drug-resistant or a therapeutic agent resistant hypercalcemic crises..

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention to use the #23-57-137-1 antibody in the treatment of hypercalcemic crises. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Potts who describe hypercalcemic crises as resulting in coma or cardiac arrest. One of skill in the art would be motivated to provide an agent which would bind to PTHrP and decrease the binding of PTHrP to the PTH receptor because Potts teaches that it is the activation of the PTH receptor by PTHrP that is responsible for hypercalcemia. One of skill in the art would be motivated to combine the teachings of Potts with the teachings of Sato et al because the abstract of Sato et al states that the #23-57-137-1 antibody, which binds to PTHrP, can be used in the treatment of hypercalcemia. It would be inherent in these teachings that said antibody were able to inhibit the binding of PTHrP to the PTH receptor. Without being able to inhibit the binding of the PTHrP to the PTH receptor, the antibody would not be effective in the treatment of hypercalcemia, and the effect would not be consistent with the teachings of Sato et al, that the antibody is useful in treating hypercalcemia.

11. Claims 22-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Sato et al (WO 9813388 and Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915) as applied to claims 22-24, 27-30 above, and further in view of Schlom (In: Molecular foundations of Oncology, Sameule Broader, Ed, 1991, pages 95-134).

The combination of Sate et al and Potts renders obvious claims 22-24, 27-30 for the reasons set forth above. Claim 25 embodies the method of claim 22 wherein the patient is administered at least one fragment of the humanized anti-PTHrP antibody. Claim 26 embodies the method of claim 25 wherein the fragment is chosen from at least one of Fab, scFV, F(ab')2 and Fv. Neither the abstract of Sato et al nor Potts et al teach the administration of antibody fragments.

Schlom teaches that F(ab')2 or Fab' fragments also help reduce the HAMA response (page 119 second column, lines 16-17 under the heading "Single Chain Antigen Binding Proteins). Schlom also teaches that scFv although comparable in binding affinity to Fab' have a more rapid plasma clearance than the Fab' fragment resulting in a greater tumor to tissue ratio. Schlom also points out that the small size of the scFv improves the capacity for penetration through the tumor mass.. Schlom also points out that scFv are easier to make than F9ab')2 of Fab' fragments.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention to use fragments of the #23-57-137-1 antibody in the treatment of hypercalcemic crises. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Schlom et al who point out that antibody fragments such as Fab' result in a greater tissue to tumor ration and that scFv have a greater ability to penetrate tumor vasculature.

12. Claims 22-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Sato et al (WO 9813388) and Potts (Diseases of the Parathyroid Gland and Other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915) and Schlom (In: Molecular foundations of Oncology, Sameule Broader, Ed, 1991,

pages 95-134).as applied to claims 22-30 above, and further in view of Grsitina et al (US 5,681,565). Claim 31 embodies the method of claims 22 or 25 wherein the antibody is bound to a carrier. claim 33 specifies that the carrier of claim 31 is PEG. Neither of the prior art references of the Sato et al abstract, nor Potts, nor Schlom teach antibodies bound to PEG as a carrier.

Gristina et al teach that antibodies can administered in a creme or ointment carrier such as oleaginous bases or polyethylene glycol for in situ use (column 5, lines 3-21).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention to use PEG as a carrier for the #23-57-137-1 antibody. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Grishina et al on the effectiveness of PEG as a carrier for in situ administration of antibodies.

13. Claims 22-30are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 126-136 and 138 of copending Application No. 09/269,332 in view of Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915) and Schlom (In: Molecular foundations of Oncology, Sameule Broader, Ed, 1991, pages 95-134).

Claims 126-136 and 138 of the '332 application teach the administration of a polypeptide comprising an L chain V region of a humanized antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NO:48-51 or 52-55.

Potts teaches that severe hypercalcemia, usually defined as 15 mg/dl or above is a medical emergency, and that coma or cardiac arrest can occur when serum calcium levels are at 15 to 18 mg/dl or higher. Potts teaches rehydration with saline as a therapeutic agent (pages 1912-1913, under the heading , and therefore fulfills the specific embodiment of physiological saline. Potts teaches phosphate administered intravenously as a therapeutic agent(pages 1913-1914, under the heading "Phosphate") and biphosphonates (page 1913, first column,), fulfilling the specific embodiment of a biphosphonate, as well as glucocorticoids (a steroid) and calcitonin (page 1913, second column). Potts does not specifically teach a drug-resistant or a therapeutic agent resistant hypercalcemic crises..

Schlom teaches that F(ab')2 or Fab' fragments also help reduce the HAMA response (page 119 second column, lines 16-17 under the heading "Single Chain Antigen Binding Proteins). Schlom also teaches that scFv although comparable in binding affinity to FAb' have a more rapid plasma clearance than the Fab' fragment resulting in a greater tumor to tissue ratio. Schlom also points out that the small size of the scFv improves the capacity for penetration through the tumor mass.. Schlom also points out that scFv are easier to make than F9ab')2 of Fab' fragments.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to treat a patient undergoing hypercalcemic crisis wherein said crises was manifest by coma or cardiac arrest by carrying out the methods of claims 126-136 and 138 in order to lower blood calcium to normal levels. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Potts regarding the risk of coma or cardiac arrest in individual having serum calcium levels of 15 mg/dl to 18 mg/ dl or higher. It would also be obvious to use a fragment of the antibody such as scFv for maximum penetration into the tumor vasculature.

Potts teaches the therapeutic agents as set forth in claim 23. None of the references specifically teach the therapeutic intervention of hypercalcemic crisis after the therapeutic agents as taught by Potts et al fail: However, one of skill in he art would be motivated to administer the antibody to patients having drug-resistant hypercalcium because it is an emergency situation, and the antibody can directly antagonize the action of the PTH receptor. One of skill in the art would be motivated to find a molecular means of intervention that was unrelated to the molecular mechanism of action of the drug or therapeutic agent which failed to maintain the patients serum calcium level within the normal range.

It is noted that claims 126-136 and 138 do not specify the administration of a humanized #23-57-137-1 antibody. however, said antibody appear to be included in the genus of antibodies upon which the '332 method claims depend. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable

differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

This is a provisional obviousness-type double patenting rejection.

14. Claims 22-32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 126-136 and 138 of copending Application No. 09/269, and Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915) and Schlom (In: Molecular foundations of Oncology, Sameule Broader, Ed, 1991, pages 95-134) as applied to claims 22-30 above and in further view of Grsitina et al (US 5,681,565).

Gristina et al teach that antibodies can administered in a creme or ointment carrier such as oleaginous bases or polyethylene glycol for in situ use (column 5, lines 3-21).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention to use PEG as a carrier for the antibodies in method claims 126-136 and 138 of application '322. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Grishina et al on the effectiveness of PEG as a carrier for in situ administration of antibodies.

15. Applicant argues that none of the references teach a method of treating hypercalcemic crises, but instead teach methods of treating simple hypercalcemia. Applicant outlines three main differences between simple hypercalcemia and hypercalcemic crises , cited first "more serious symptomology", and secondly "greater levels of blood calcium. Applicant argues that current methods for treating hypercalcemia are not effective for treating hypercalcemic crises as the third "difference" between hypercalcemic crises and simple hypercalcemia. This has been considered but not found persuasive. The difference between hypercalcemia caused by an excess of PTHrP and hypercalcemic crises caused by an excess in PTHrP over the level of about 15 mg/dl to 18 mg/dl is only a matter of degree. One of skill in the art would recognize that inhibiting the binding of PTHrP to the PTH receptor by the administration of an antibody which

inhibits the binding of PTHrP to the PTH receptor will be therapeutic for the treatment of hypercalcemia caused by an excess of PTHrP.

Applicant argues that none of the cited references in the previous Office action teach a humanized antibody. In the instant application, Sato et al teaches the administration of humanized !23-57-137-1 which is the same as that claimed. Further, there would be ample motivation to make a humanized antibody from a rodent antibody for the administration of humans in order to avoid the HAMA response as taught by Schlom.

16. All other rejections and objections as set forth in the previous Office action are withdrawn.

Conclusion

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (571) 272-0828. The examiner can normally be reached on Monday through Friday from 9 am to 6:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Primary Examiner, Group 1642
01/23/04